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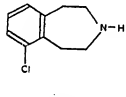
(54) NEW TETRAHYDROAZEPINE DERIVATIVE, PROCESS FOR ITS PRODUCTION AND COMPOSITIONS CONTAINING SAME

(71) We, J. R. GEIGY A.G., a body corporate organised according to the laws of Switzerland, of 215, Schwarzwaldallee, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention concerns a new tetrahydroazepine derivative, its pharmaceutically acceptable addition salts with inorganic or organic acids, a process for the production of the new compound, medicines containing the latter and the application of these medicines.

The 6 - chloro - 2,3,4,5 - tetrahydro - 1H-3 - benzazepine of formula I



(I)

and its pharmaceutically acceptable addition salts with inorganic and organic acids have not been known hitherto.

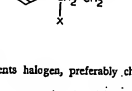
It has now been found that these new substances possess valuable pharmacological properties, having for example an anorexigenic action.

6 - Chloro - 2,3,4,5 - tetrahydro - 1H-3 - benzazepine and its acid addition salts are produced in accordance with the invention, by reacting chlorine with 2,3,4,5 - tetrahydro - 1H - 2 - benzazepine under normal standard conditions for the chlorination of aromatic rings, separating the desired 6-chloro - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine from the reaction mixture directly or after conversion into an addition salt with an inorganic or organic acid, and if desired, converting the base or an initially obtained non-pharmaceutically acceptable acid addition salt into an acid addition salt which is pharmaceutically acceptable.

The chlorination according to the invention is carried out for example in the presence of catalysts such as aluminium chloride, zinc chloride, iron (III)-chloride, iron wire turnings or iodine in the presence or absence of solvents such as, for example, nitrobenzene or glacial acetic acid. The chlorination is performed for example at temperatures between 10 and 120° C. It is particularly suitable to effect chlorination by using a reaction mixture of aluminium chloride and 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine, obtained in the manner given in more detail below, at elevated temperatures, preferably between 70 and 100°C.

The 6 - chloro - 2,3,4,5 - tetrahydro - 1H-3 - benzazepine is separated from the crude chlorination products for example by fractional crystallisation of one of its salts, e.g. the hydrochloride, from suitable organic solvents or solvent mixtures, such as for example ethanol or ethanol/ethylacetate.

The 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine used as the starting material is known and can be produced using various processes. It is particularly advantageous, however, to produce it using a process hitherto unknown. Compounds of the general formula II



(II)

wherein

X represents halogen, preferably chlorine or

bromine, or addition salts of these compounds with inorganic or organic acids can surprisingly be condensed by means of Lewis acids to obtain 2,3,4,5 - tetrahydro - 1H - 3-benzazepine.

Lewis acids suitable for the above process are for example: antimony(V)-chloride, iron-(III)-chloride, tellurium (II)-chloride, tin(IV)-chloride, titanium(IV)-chloride, tellurium-(IV)-chloride, bismuth(III)-chloride, zinc chloride and particularly aluminium chloride, as well as corresponding bromides and iodides, also borotrifluoride or borotrichloride, hydrogen fluoride, sulphuric acid, phosphorus pentoxide or polyphosphoric acid. The Lewis acid is usually added to the extent of 0.05—5 mol %, preferably 1—1.5 mol %, to the reaction mixture. The reaction temperatures with the Lewis acid are desirably between 100 and 300°C, preferably between 150 and 250°C. The 2,3,4,5 - tetrahydro - 1H - 3-benzazepine formed is then isolated by addition of a base, preferably an inorganic base, e.g. an alkali metal hydroxide, such as sodium or potassium hydroxide, to the reaction mixture.

In general, the reaction of a compound of the general formula II with a Lewis acid does not require a solvent or diluent. If desired however, it is possible to use as such for example, a nitrohydrocarbon, such as nitrobenzene, or a halogen hydrocarbon, such as *o*-dichlorobenzene.

The Friedel-Crafts catalysts, which are preferably used as Lewis acids, in particular aluminium chloride, are also suitable catalysts for the chlorination of aromatic rings in aromatic compounds with aliphatic side chains or fused saturated rings. Optionally it is therefore possible to eliminate the step of isolating the 2,3,4,5 - tetrahydro - 1H - 3-benzazepine and, in accordance with a particularly advantageous method of application of the process according to the invention, to use directly the reaction mixtures obtained after ring closure of the compounds of the general formula II, to prepare the 6 - chloro-2,3,4,5 - tetrahydro - 1H - 3 - benzazepine, using Friedel-Crafts catalysts, particularly aluminium chloride. In this case, the previously mentioned isolation of the ring closure product resulting from the addition of a base to the reaction mixture, occurs only following chlorination according to the invention.

The N - [(2 - chloro - ethyl) - phenethylamine] - hydrochloride, an addition salt of a compound of the general formula II, can for example be produced as follows: by reacting styrene in the presence of sodium with ethylene imine, to form 1-phenethyl-aziridine and adding hydrogen chloride to this aziridine, which is dissolved in methanol. The remaining compounds of the general formula II can be produced in an analogous manner.

The 6 - chloro - 2,3,4,5 - tetrahydro - 1H-3 - benzazepine obtained by chlorination according to the invention, is converted either directly as the crude product into an acid addition salt, in particular the hydrochloride, suitable for fractional crystallisation, or else it is firstly purified by methods known in the art and subsequently converted into an addition salt with an inorganic or organic acid. For example, a solution of 6 - chloro - 2,3,4,5-tetrahydro - 1H - 3 - benzazepine in an organic solvent is mixed with the acid which is desired as the salt constituent, or with a solution of this acid. Preferably, organic solvents are chosen for the reaction, in which the desired salt is not readily soluble, so that it can be separated off by filtration. Such solvents are for example methanol, acetone, methylethyl ketone, acetone/ethanol, methanol/ether and ethanol/ether.

In order, subsequently, to transform any acid addition salt into another, especially a pharmaceutically acceptable one, either the base is firstly liberated and converted as above into another salt, or the salt is reacted directly with another acid or a salt thereof in a suitable medium, in which it is more readily soluble than the salt desired.

For application as medicaments, a pharmaceutically acceptable acid addition salt may be used instead of the free base, e.g. salts with acids whose anions are not toxic at the required dosage. It is moreover advantageous, if the salts to be used as medicaments are easily crystallizable and are not, or are only slightly, hygroscopic. For forming a salt with 6 - chloro - 2,3,4,5 - tetrahydro - 1H - 3-benzazepine, it is possible to use for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, β-hydroxyethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, mandelic acid and embonic acid.

The new active substances are administered orally, rectally or parenterally. The daily dosages of the free base or of pharmaceutically acceptable salts thereof vary between 25 and 200 mg for adult patients. Suitable dosage units, such as dragées (sugar coated tablets), tablets, suppositories or ampoules, contain preferably 5—50 mg of the active substance according to the invention, or of a pharmaceutically acceptable salt thereof.

Dosage units for oral administration preferably contain as active substance between 1—90% of 6 - chloro - 2,3,4,5 - tetrahydro-1H - 3 - benzazepine or a pharmaceutically acceptable acid addition salt thereof. They are produced by combining the active substance with, e.g., solid pulverulent carriers, such as lactose, saccharose, sorbitol, mannitol; starches such as potato starch, maize starch

or amylopectin, also laminaria powder or citrus pulp powder; cellulose derivatives or gelatine, optionally with the addition of lubricants, such as magnesium or calcium stearate or polyethylene glycols, to form tablets or dragée cores. The latter are coated, e.g., with concentrated sugar solutions, which can also contain, e.g., gum arabic, talcum and/or titanium dioxide, or with a lacquer dissolved in easily volatile organic solvents or mixtures of solvents. Dyestuffs can be added to these coatings, e.g. to distinguish between various dosages of active substance.

Other suitable dosage units for oral administration are hard gelatine capsules, and also soft closed capsules made of gelatine and a softener such as glycerin. The hard gelatine capsules preferably contain the active substance as a granulate, e.g. in admixture with fillers, such as maize starch, and/or lubricants, such as talcum or magnesium stearate, and, optionally, stabilisers such as sodium metabisulphite ($Na_2S_2O_5$) or ascorbic acid. In soft capsules, the active substance is preferably dissolved or suspended in suitable liquids, such as liquid polyethylene glycols, whereby stabilisers can also be added.

Examples of dosage units for rectal administration are, e.g., suppositories comprising the active substance or a suitable salt thereof with a fatty base, or also gelatine rectal capsules, which contain a combination of the active substance or a suitable salt thereof, with polyethylene glycols.

Ampoules for parenteral, particularly intramuscular, administration preferably contain a water soluble salt of the active substance in a concentration of, preferably, 0.5—5%, in aqueous solution, optionally together with suitable stabilisers and buffer substances.

The following prescriptions further illustrate the production of tablets and dragées:

a) 250 g of 6 - chloro - 2,3,4,5 - tetrahydro-1H - 3 - benzazepine hydrochloride are mixed with 175.80 g of lactose and 169.70 g of potato starch, the mixture being moistened with an alcoholic solution of 10 g of stearic acid and granulated through a sieve. After drying, 160 g of potato starch, 200 g of talcum, 2.50 g of magnesium stearate and 32 g of colloidal silicon dioxide are mixed in and the mixture is pressed into 10,000 tablets, each weighing 100 mg and containing 25 mg of active substance, which, if desired, can be grooved for finer adjustment of the dosage.

b) A granulate is produced from 250 g of 6 - chloro - 2,3,4,5 - tetrahydro - 1H - 3-benzazepine hydrochloride, 175.90 g of lactose and an alcoholic solution of 10 g of stearic acid. After drying, the granulate is mixed with 56.60 g of colloidal silicon dioxide, 165 g of talcum, 20 g of potato starch and 2.50 g of magnesium stearate and the mixture is pressed into 10,000 dragée cores. These are then coated with a concentrated syrup made from 502.28 g of crystallised saccharose, 6 g of shellac, 10 g of gum arabic, 0.22 g of dyestuff and 1.5 g of titanium dioxide and dried. The obtained dragées each weigh 120 mg and each contain 25 mg of active substance.

The following examples further illustrate the production of 6 - chloro - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine and its acid addition salts but they in no way restrict the scope of the invention. The temperatures are given in degrees centigrade.

Example 1

1105 g of N - (2 - chloroethyl) - phenethylamine hydrochloride (=5 mol) are mixed wirth 1000 g of aluminium chloride (=7.5 mol), and the mixture heated slowly whilst stirring to 180° (bath temperature) and held for 14 hours at this temperature. After this period of time the HCl evolution has finished.

The reaction mixture obtained, which contains the crude 2,3,4,5 - tetrahydro - 1H - 3-benzazepine, is cooled to 80° and, over a period of 4 hours at 80°, 415 g of chlorine gas (=5.8 mol) are introduced. The melt is poured still hot on to ice and stirred until solution has occurred. Whilst stirring and with slight cooling, 7000 ml of 30% conc. sodium hydroxide solution are then added. The mixture is stirred at room temperature until the precipitated aluminium hydroxide has again completely dissolved. The solution is then extracted with 20 l of ether in 4 portions, the combined ether solutions being dried over potassium carbonate/magnesium sulphate and the solution evaporated after filtering off the drying agent. Fractional distillation of the oily evaporation residue produces monochlorinated 2,3,4,5-tetrahydro-1H-3-benzazepine in the boiling range of 81—84°/0.08 Torr and with a refractive index of n_D^{20} 1.579—1.581 as the major fraction.

In further processing, 100 g of the above major fraction are dissolved in 1000 ml of abs. ether and the solution mixed with 200 ml of absolute-ethereal 3N hydrogen chloride solution. The precipitated crude monochlorinated 2,3,4,5 - tetrahydro - 1H - 3-benzazepine hydrogen chloride is filtered off and recrystallised firstly twice from ethanol/ethylacetate (1:2, then 1:1) and then four times from abs. ethanol (180, 150, 100 and 100 ml). The desired 6 - chloro - 2,3,4,5-tetrahydro - 1H - 3 - benzazepine hydrochloride of M.P. 216—217° is thereby obtained, the NMR-spectrum of which corresponds to the stated constitution.

The crude base is liberated from the mother liquor and distilled under high vacuum, Kp. 69—72°/0.07 Torr. The distillate in 500 ml of abs. ether is mixed with the calculated quantity of 3N hydrogen chloride solution

in ether. The crude hydrochloride obtained is again filtered off and recrystallised four times from abs. ethanol, whereby further 6-chloro - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine hydrochloride is obtained of M.P. 214—215°.

EXAMPLE 2

221 g of N - (2 - chloroethyl) - phenethylamine hydrochloride (=1 mol) are mixed intimately with 200 g of anhydrous aluminium chloride (=1.5 mol) and the mixture slowly heated to 170° (bath temperature), held for 6 hours at this temperature and heated for a further 8 hours at 180° (bath temperature).

After cooling to 90°, 85 g of chlorine gas (=1.1 mol) are passed through the obtained reaction mixture containing the crude 2,3,4,5-tetrahydro - 1H - 3 - benzazepine over a period of 2 hours at an internal temperature of 90—95°. The reaction mixture is then poured hot onto ice, stirred for 1 1/2 hours at room temperature, until complete solution has occurred and then rendered alkaline by addition of 1000 ml of 30% conc. sodium hydroxide solution. After the initially precipitated aluminium hydroxide has dissolved, the solution is extracted four times with 800 ml of diethyl ether each time. The combined extracts are dried (potassium carbonate / magnesium sulphate) and evaporated to an oil residue. Fractionation in high vacuum produces crude monochlorinated 2,3,4,5 - tetrahydro - 1H - 3-benzazepine as the principal fraction, with a boiling range of about 75—85° at 0.02—0.08Torr. Refractive index n_D20 about 1.579.

Preparation of the principal fraction is carried out completely analogously to Example 1.

WHAT WE CLAIM IS:—

1. Process for the production of a new tetrahydroazepine derivative of formula I

(I)

and its addition salts with inorganic and organic acids, characterised by reacting chlorine with 2,3,4,5 - tetrahydro - 1H - 3-benzazepine, separating off the desired 6-chloro - 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine from the reaction mixture directly or after conversion into an addition salt with an inorganic or organic acid, and converting, if desired, the free base into a pharmaceutically acceptable acid addition salt, or an initially obtained non-pharmaceutically acceptable addition salt into an acid addition salt which is pharmaceutically acceptable.

2. Process as claimed in claim 1 in which the 2,3,4,5 - tetrahydro - 1H - 3 - benzazepine has been produced by condensation of a compound of formula II

in which X represents an halogen or inorganic or organic acid addition salts of these compounds, in the presence of a Lewis acid.

3. 6 - Chloro - 2,3,4,5 - tetrahydro - 1H-3 - benzazepine and its pharmaceutically acceptable addition salts with inorganic or organic acids.

4. 6 - Chloro - 2,3,4,5 - tetrahydro - 1H-3 - benzazepine hydrochloride.

5. A new tetrahydro azepine derivative of general formula I as defined in claim 1, substantially as herein described with reference to and as illustrated in any of the foregoing examples.

6. Process according to claim 1, substantially as herein described with reference to and as illustrated in any of the foregoing examples.

7. Pharmaceutical compositions for the treatment of obesity, characterised by a content of 6 - chloro - 2,3,4,5 - tetrahydro - 1H-3 - benzazepine or of a pharmaceutically acceptable acid addition salt thereof in combination with an inert and pharmaceutically acceptable carrier.

8. Compositions as claimed in claim 7, substantially as hereinbefore described.

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